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EXAMINER	
POPA, ILEANA	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,909	BRON, DENIS	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,9-11,13-15,17-19,21-25 and 27-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9-11,13-15,17-19,21,27 and 29* is/are rejected.

7)☒ Claim(s) *22-25 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/30/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4, 7, 8, 12, 16, 20, and 26 have been cancelled. Claims 1, 5, 21, 22, 24, and 28 have been amended. Claim 29 is new.

Claims 1-3, 5, 6, 9-11, 13-15, 17-19, 21-25, and 27-29 are pending and under examination.

2. All rejections/objections pertaining to claims 4, 7, 8, 12, 16, 20, and 26 are moot because Applicant cancelled the claims in the reply filed on 06/30/2008.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to the foreign application EPO 02014991.0. However, the disclosure of the foreign application EPO 02014991.0, fails to provide adequate support or enablement for one or more claims of this application.

The instant claims disclose a delivery system comprising the NCAM Ig loop domains I, II, and III, wherein the delivery system further comprises an integrase, wherein the integrase is from the phiC31 bacteriophage. The Application EPO 02014991.0 does not provide support for the use of the NCAM Ig loop domains I, II, and III or for the use of any integrase. Therefore, the priority date for these embodiments is considered to be the filing date of the PCT/CH03/00453, i.e., 07/08/2003.

Should Applicant disagree, Applicant is encouraged to point out with particularity

by page and line number where such support might exist in each intervening document. In order to properly claim priority, the support for each of the claim limitations must exist in each of the intervening documents.

Information Disclosure Statement

3. Acknowledgment is made of Applicant's submission of an IDS form of 06/30/2008 has been. It is noted that, since Applicant did not provide an English translation, the foreign document DE 100 56 136 was only considered with respect to its abstract.

Response to Arguments

Claim Objections

4. The objections to claims 5, 6, 9-11, 13-15, 17-19, and 21 as being in improper form are withdrawn in response to Applicant's amendments to the claims filed on 06/30/2008.

Applicant points out that, although the Examiner indicated claim 2 as being multiple dependent, he believes that the objection was intended to refer to the multiple dependent claim 3, because claim 3 was filed as a multiple dependent claim whereas claim 2 was not. It is noted that Applicant is right; the objection was meant to refer to claim 3. In the Office action of 01/02/200, the Examiner erroneously indicated claim 2 as multiple dependent; the Examiner meant to indicate claim 3 as multiple dependent.

5. Claims 22-25 and 28 remain objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot serve as a basis for any other multiple dependent claims, either directly or indirectly. In the instant case, the multiple dependent claims 22-25 and 28 directly or indirectly depend from the multiple dependent claim 21. See MPEP § 608.01(n).

Accordingly, claims 22-25 and 28 remain withdrawn from examination and are not being treated on the merits.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The rejection of claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al. (PGPUB 2005/0037445), in view of each Maurer et al. (Expert Opin Biol Ther, 2001, 1: 923-947), Ranheim et al. (Proc Natl Acad Sci USA, 1996, 93: 4071-4075), and Schreier et al. (J Biol Chem, 1994, 269: 9090-9098) is withdrawn in response to Applicant's amendment to the claims filed on 06/30/2008. Specifically, Applicant amended claim 1 to recite that the delivery system comprises a DNA encoding an integrase activity, limitations which is not taught by the combination of the art cited above.

8. The rejection of claims 1 and 2 under 35 U.S.C. 103(a) as being unpatentable over Murphy (U.S. Patent No. 6,635,476), in view of Poulsen et al. and Ranheim et al. is withdrawn in response to Applicant's amendment to the claims filed on 06/30/2008. Specifically, Applicant amended claim 1 to recite that the delivery system comprises a DNA encoding an integrase activity, limitations which is not taught by the combination of the art cited above.

New Rejections

Claim Rejections - 35 USC § 112, new matter

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-3, 5, 6, 9, 10, 13, 14, 17, 18, 21, and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, the amendment to the claim to include the term "a DNA integrase activity" is considered new matter.

As amended claim 1 recites the use of "a DNA integrase activity or a molecule encoding such a DNA integrase activity". It is clear from the claim language that the "DNA integrase activity" is the protein. It is noted that the specification only provides support for the use of a nucleic acid encoding an integrase; there is no support for the use of the protein (see p. 4, lines 1-13). A search of the remaining portions of the specification failed to provide literal support for the use of integrase protein.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-3, 5, 6, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al. (PGPUB 2005/0037445, of record), in view of each Maurer et al. (Expert Opin Biol Ther, 2001, 1: 923-947, of record), Groth et al. (Proc. Natl. Acad. Sci. USA, 2000, 97: 5995-6000), Schreier et al. (J Biol Chem, 1994, 269: 9090-9098, of record), and Ranheim et al. (Proc Natl Acad Sci USA, 1996, 93: 4071-4075, of record).

Poulsen et al. teach a delivery system for cDNAs encoding therapeutic proteins (i.e., pharmaceutical agents) the system comprising the cDNAs operably linked to a gene expression construct, a binding partner capable of associating with a cell surface receptor (i.e., a targeting moiety), and polycations, wherein the polycations form particles comprising the nucleic acid in their internal compartment and wherein the polycations form a bridge between the nucleic acid and the targeting moiety, i.e., the targeting moiety is on the particle surface (claims 1, 5, and 6) (p. 33, paragraphs 0390-0394, p. 34, paragraphs 0412-0418, p. 39, paragraphs 0563-0565, 0570, 0571, and 0577). Poulsen et al. teach that the targeting moiety can be NCAM or NCAM IgI+II or IgIII domains (claim 1) (p. 26, paragraph 0264, p. 29, paragraph 0335, p. 30, paragraphs 0346, 0355, and 0357, p. 31, paragraphs 0358-0360).

Although Poulsen et al. teach that liposomes in general could be used to deliver nucleic acids (p. 1, paragraph 0004), they do no specifically teach liposomes as the bridge between the nucleic acid and the targeting moiety (claim 1). Maurer et al. teach liposomes as the leading delivery system for the *in vivo* administration of nucleic acids (Abstract, p. 941, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Poulsen et al. by substituting the polycations with liposomes, with a reasonable expectation of success. The motivation to do so is provided by Maurer et al., who teach liposomes as the leading delivery system for systemic administration of nucleic acids, wherein liposomes are versatile carriers because they can be easily modified by insertion of diverse molecules, such as targeting ligands, to suit any particular application (p. 923, column 1, p. 926, paragraph bridging p. 927, p. 927, column 1, last paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that liposomes can be successfully used to target nucleic acids to the cell/tissue of interest.

Although Poulsen et al. and Maurer et al. teach targeting liposomes by using an NCAM fragment comprising the IgI and IgII domains or an NCAM fragment comprising IgIII domain as targeting ligands, they do not teach using a fragment comprising all IgI, IgII, and IgIII domains of NCAM (claim 2). However, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al. and Maurer et al. by combining their IgI, IgII, and IgIII domains into one fragment for increased binding to NCAM on the target cell surface, with a reasonable

expectation of success. One of skill in the art would have been motivated to do so because the art teaches that, beside the IgI and IgII domains, the IgIII domain also contributes to the binding to NCAM (see Poulsen et al., p. 31, paragraphs 0358-0360; Ranheim et al., p. 4074, column 2, and Fig. 6). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that all three Ig NCAM domains are involved in homophilic binding to the NCAM molecule expressed on the surface of the target cell.

Poulsen et al., Maurer et al., and Ranheim et al. do not teach a nucleic acid encoding the phiC31 integrase (claims 1 and 27). However the prior art teaches site-specific integration into mammalian cell genome for research and gene therapy, wherein site-specific integration is used to avoid undesirable mutations in important genes and wherein specific and efficient site-specific integration is achieved by using the phiC31 integrase (see Groth et al., Abstract, p. 5995, column 2, p. 5998, p. 5999, columns 1 and 2, p. 6000, columns 1 and 2). Based on these teachings, one of skill in the art would have known to use phiC31 integrase when the stable and specific integration of genes of interest into the genome of a target cell was required. Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al. and Maurer et al. by further including the phiC31 integrase, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain stable and targeted integration of transgenes into a target cell for research or gene therapy purposes. One of skill in the art would have been expected to have a reasonable expectation of success in doing so

because the prior art teaches phiC31 integrase can be successfully used to direct site-specific integration of transgenes into the genome of mammalian cells (see Groth et al., p. 6000, column 1).

Poulsen et al., Maurer et al., Ranheim et al., and Groth et al. do not teach linking the NCAM via a hydrophobic anchor molecule (claim 3). However, such is suggested by the prior art. For example, Schreier et al. teach targeting liposomes to specific cells by inserting ligands into liposomes via a glycosylphoshaphatidylinositol (GPI) anchor (i.e., a hydrophobic anchor molecule) (Abstract, p. 9092, columns 1 and 2, p. 9093, columns 1 and 2, p. 9097, column 1, paragraph bridging column 2, 9098, column 1, last paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al. and Maurer et al. by inserting the NCAM ligand via a GPI anchor, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Schreier et al. teach their method as simple and convenient (p. 9090, column 2, first full paragraph). One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful use of GPI anchors to incorporate proteins into liposomes.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they pertain to the instant rejection:

Applicant argues that Poulsen et al. do not specifically teach liposomes as a bridge between the DNA and the targeting moiety, i.e., liposomes comprising DNA in their internal compartment and having NCAM or a fragment thereof on their surface. In response to this argument, it is noted that the instant rejection is an obviousness-type rejection which is based on a combination of references; it is the combination of reference which teaches liposomes having DNA in their internal compartment and NCAM on their surface. Because the instant rejection is an obviousness-type rejection, Poulsen et al. do not have to teach each and every claim limitation; if they did, the rejection would have been anticipation and not an obviousness-type rejection.

The rest of Applicant's arguments are directed to the recitation "a DNA integrase activity" in the newly amended claims and do not pertain to the instant rejection.

13. Claims 1-3, 5, 6, 9, 10, 13, 14, 17, 18, 21, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al. taken with each Maurer et al., Groth et al., Schreier et al., and Ranheim et al., in further view of each Sato et al. (J. Drug Target., 2001, 9: 201-207) and Gosselin et al. (Bioconjugate Chem., 2001, 12: 989-994).

The teachings of Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. are applied as above for claims 1-3, 5, 6, and 27. Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. do not teach their delivery system as further comprising a DNA compacting agent (claims 9 and 10), nor do they teach a chemical inclusion for breaching the endosomal barrier (claim 21). Sato et al. teach that

introducing cationic polymers such as high molecular weight PEI into DNA/liposome complexes enhances their transfection efficiency by condensing the DNA and promoting the escape of the DNA from the endosomal compartment (i.e., PEI breaches the endosomal barrier) (p. 202, column 1, last paragraph, and column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the system of Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. according to the teachings of Sato et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do because the art teaches that addition of PEI enhance the transfection efficiency of complexes made only of DNA and liposomes.

Poulsen et al., Maurer et al., Groth et al., Schreier et al., Ranheim et al., and Sato et al. do not teach their PEI as being reversibly cross-linked via a thio bridge (claims 13, 14, 17, and 18). Gosselin et al. teach replacing the cytotoxic high molecular PEI with conjugates consisting of low molecular weight PEI cross-linked via thio bridges, wherein such conjugates are less cytotoxic because the thio bridges are cleaved in the reducing environment of the cytoplasm resulting in less cytotoxic intracellular low molecular weight PEI which has an easier access to the transcription machinery (Abstract, p. 989, column 2, p. 990, Fig. 1 and 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al., Maurer et al., Groth et al., Schreier et al., Ranheim et al., and Sato et al. by replacing their high molecular weight PEI with the cross-linked low molecular weight PEI of Gosselin et al., with a reasonable expectation of success. One of skill in the art

would have been motivated to do so in order to obtain a less cytotoxic DNA delivery system. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that cross-linked low molecular weight PEI can be successfully used to deliver DNA to cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

14. Claims 1, 2, 5, 6, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy (U.S. Patent No. 6,635,476, of record), in view of each Poulsen et al., Ranheim et al., and Groth et al.

Murphy teaches a system for the delivery of genes encoding therapeutic polypeptides (i.e., cDNA operably linked to a gene expression construct), the system comprising liposomes having the gene in their internal space and targeting ligands on their external surface for binding to specific cell surface receptors, wherein the receptors can be NCAM (claims 1, 5, and 6) (Abstract, column 3, lines 5, 6, and 59-63, column 5, lines 24-27, column 9, lines 45-63, column 13, lines 25-46).

Although Murphy teaches NCAM as the cell surface receptor, he does not specifically teach that the targeting ligand is NCAM or an NCAM fragment comprising the first three Ig domains as targeting ligands (claims 1 and 2). Poulsen et al. teach NCAM and NCAM fragments comprising the IgI and IgII domains or the IgIII domain as targeting ligands capable of homophilic binding to another NCAM molecule on the surface of a target cell (p. 3, paragraph 0036, p. 4, paragraphs 0048-0051, p. 28,

paragraphs 0288 and 0290, p. 29, paragraphs 0355, p. 31, paragraphs 0358-0360). It would have been obvious to one of skill in the art, at the time the invention was made, to modify Murphy's delivery system by using one of the targeting ligands taught by Poulsen et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Murphy teaches delivery to cells expressing NCAM on their surface and because Poulsen et al. teach their fragments as capable of specific delivery to NCAM-expressing cells. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because Murphy teaches that any ligand that binds NCAM can be used with their system (column 13, lines 50-61). With respect to the limitation recited in claim 2, it would have been obvious to one of skill in the art, at the time the invention was made, to combine the IgIII and IgI+IgII fragments of Poulsen et al. to obtain an IgI+IgII+IgIII fragment, for increased binding to NCAM on the target cell surface, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because the art teaches that, besides the beside IgI and IgII domains, the IgIII domain, also contributes to the binding to NCAM (see Poulsen et al., p. 31, paragraphs 0358-0360; Ranheim et al., p. 4074, column 2, and Fig. 6). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that all three Ig NCAM domains are involved in homophilic binding to the NCAM molecule expressed on the surface of the target cell.

Murphy, Poulsen et al., Ranheim et al. do not teach a nucleic acid encoding the phiC31 integrase (claims 1 and 27). However the prior art teaches site-specific

integration into mammalian cell genome for research and gene therapy, wherein site-specific integration is used to avoid undesirable mutations in important genes and wherein specific and efficient site-specific integration is achieved by using the phiC31 integrase (see Groth et al., Abstract, p. 5995, column 2, p. 5998, p. 5999, columns 1 and 2, p. 6000, columns 1 and 2). Based on these teachings, one of skill in the art would have known to use phiC31 integrase when the stable and specific integration of genes of interest into the genome of a target cell was required. Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al. and Maurer et al. by further including the phiC31 integrase, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain stable and targeted integration of transgenes into a target cell for research or gene therapy purposes. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the prior art teaches phiC31 integrase can be successfully used to direct site-specific integration of transgenes into the genome of mammalian cells (see Groth et al., p. 6000, column 1).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

It is noted that none of the Applicant's arguments pertain to the instant rejection.

15. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al., in view of each Maurer et al., Smith et al. (U.S. Patent No. 6,329,501), and Charlton et al. (Developmental Biology, 2000, 221: 112-119).

Poulsen et al. teach a delivery system for cDNAs encoding therapeutic proteins (i.e., pharmaceutical agents) the system comprising the cDNAs operably linked to a gene expression construct, a binding partner capable of associating with a cell surface receptor (i.e., a targeting moiety), and polycations, wherein the polycations form particles comprising the nucleic acid in their internal compartment and wherein the polycations form a bridge between the nucleic acid and the targeting moiety, i.e., the targeting moiety is on the particle surface (p. 33, paragraphs 0390-0394, p. 34, paragraphs 0412-0418, p. 39, paragraphs 0563-0565, 0570, 0571, and 0577). Poulsen et al. teach that the targeting moiety can be NCAM or NCAM IgI+II or IgIII domains (p. 26, paragraph 0264, p. 29, paragraph 0335, p. 30, paragraphs 0346, 0355, and 0357, p. 31, paragraphs 0358-0360).

Although Poulsen et al. teach that liposomes in general could be used to deliver nucleic acids (p. 1, paragraph 0004), they do no specifically teach liposomes as the bridge between the nucleic acid and the targeting moiety (claim 1). Maurer et al. teach liposomes as the leading delivery system for the *in vivo* administration of nucleic acids (Abstract, p. 941, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Poulsen et al. by substituting the polycations with liposomes, with a reasonable expectation of success. The motivation to do so is provided by Maurer et al., who teach liposomes as the leading delivery

system for systemic administration of nucleic acids, wherein liposomes are versatile carriers because they can be easily modified by insertion of diverse molecules, such as targeting ligands, to suit any particular application (p. 923, column 1, p. 926, paragraph bridging p. 927, p. 927, column 1, last paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that liposomes can be successfully used to target nucleic acids to the cell/tissue of interest.

Although Poulsen et al. and Maurer et al. teach delivery of therapeutic transgenes, they do not specifically teach a transgene encoding the human dystrophin. Smith et al. teach using liposomes coated with targeted ligands to specifically deliver the dystrophin gene to the muscle cells of patients suffering from Duchenne muscular dystrophy (Abstract, column 2, lines 50-60, column 5, lines 62-67, column 5, lines 3-10). Although Smith et al. do not specifically teach targeting by using NCAM or a fragment thereof, the prior art teaches that muscle cells express NCAM on their surface (see Charlton et al., Abstract, p. 112, column 2). Based on these teachings in the art as a whole, one of skill in the art would have known that the delivery system of Poulsen et al. and Maurer et al. (i.e., liposomes coated with NCAM or fragments thereof) could be used to deliver transgenes to muscle cells. Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to use the system of Poulsen et al. and Maurer et al. to deliver the dystrophin gene of Smith et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to treat patients affected by Duchenne muscular dystrophy, as taught by Smith et

al. One of skill in the art would have been expected to have a reasonable expectation of success in using NCAM-coated liposomes to target transgenes to the muscle cells expressing NCAM on their surface because the art teaches that NCAM is involved in homophilic binding to other NCAM molecules (see Poulsen et al., p. 31, paragraphs 0358-0360).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

16. Claims 11, 15, 19, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al., in view each Maurer et al., Smith et al., and Charlton et al., in further view of both Sato et al. and Gosselin et al.

The teachings of Poulsen et al., Maurer et al., Smith et al., and Charlton et al. are applied as above for claim 29. Poulsen et al., Maurer et al., Smith et al., and Charlton et al. do not teach their delivery system as further comprising a DNA compacting agent (claim 11). Sato et al. teach that introducing cationic polymers such as high molecular weight PEI into DNA/liposome complexes enhances their transfection efficiency by condensing the DNA and promoting the escape of the DNA from the endosomal compartment (i.e., PEI breaches the endosomal barrier) (p. 202, column 1, last paragraph, and column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the system of Poulsen et al., Maurer et al., Smith et al., and Charlton et al. according to the teachings of Sato et al., with a reasonable expectation of success. One of skill in the art would have been motivated to

do because the art teaches that addition of PEI enhance the transfection efficiency of complexes made only of DNA and liposomes.

Poulsen et al., Maurer et al., Smith et al., Charlton et al., and Sato et al. do not teach their PEI as being reversibly cross-linked via a thio bridge (claims 13, 14, 17, and 18). Gosselin et al. teach replacing the cytotoxic high molecular PEI with conjugates consisting of low molecular weight PEI cross-linked via thio bridges, wherein such conjugates are less cytotoxic because the thio bridges are cleaved in the reducing environment of the cytoplasm resulting in less cytotoxic intracellular low molecular weight PEI which has an easier access to the transcription machinery (Abstract, p. 989, column 2, p. 990, Fig. 1 and 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al., Maurer et al., Smith et al., Charlton et al., and Sato et al. by replacing their high molecular weight PEI with the cross-linked low molecular weight PEI of Gosselin et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain a less cytotoxic DNA delivery system. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that cross-linked low molecular weight PEI can be successfully used to deliver DNA to cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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